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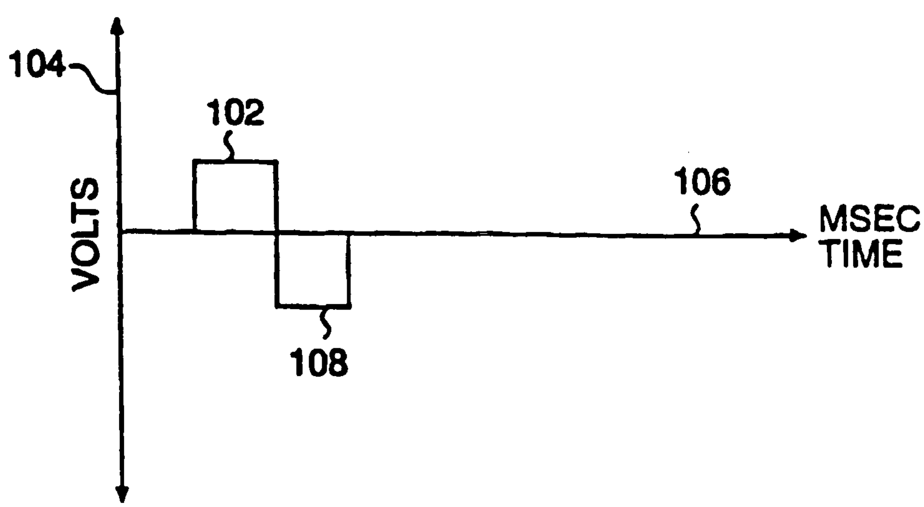

(57) Abstract

Augmentation of electrical conduction and contractibility by biphasic cardiac pacing. A first stimulation phase is administered to the cardiac blood pool. This first stimulation phase has a predefined polarity, amplitude and duration. A second stimulation phase is then administered to the cardiac blood pool. This second phase also has a predefined polarity, amplitude and duration. The two phases are applied sequentially. Contrary to current thought, anodal stimulation is first applied and followed by cathodal stimulation. In this fashion, pulse conduction through the cardiac muscle is improved together with the increase in contractibility.

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AUGMENTATION OF ELECTRICAL CONDUCTION AND CONTRACTILITY BY BIPHASIC CARDIAC PACING ADMINISTERED VIA THE CARDIAC BLOOD POOL

Inventor: Morton M. Mower, M.D.

RELATED APPLICATION DATA

The present disclosure is a continuation-in-part application related to the U.S. Patent Application entitled "Augmentation of Electrical Conduction and Contractility by Biphasic Cardiac Pacing", Serial No. 08/699,552, filed August 8, 1996.

FIELD OF THE INVENTION

This invention relates generally to a method for the stimulation of muscle tissue. In particular, this invention relates to a method for cardiac stimulation and pacing with biphasic waveforms wherein the stimulation is administered via the cardiac blood pool.

BACKGROUND OF THE INVENTION

The function of the cardiovascular system is vital for survival. Through blood circulation, body tissues obtain necessary nutrients and oxygen, and discard waste substances. In the absence of circulation, cells begin to undergo irreversible changes that lead to death. The muscular contractions of the heart are the driving force behind circulation.

In cardiac muscle, the muscle fibers are interconnected in branching networks that spread in all directions through the heart. When any portion of this net is stimulated, a depolarization wave passes to all of its parts and the entire structure contracts as a unit. Before a muscle fiber can be stimulated to contract, its membrane must be polarized. A muscle fiber generally remains polarized until it is stimulated by some change in its environment. A membrane can be stimulated electrically, chemically, mechanically or by temperature change. The minimal stimulation strength needed to elicit a contraction is

known as the threshold stimulus. The maximum stimulation amplitude that may be administered without eliciting a contraction is the maximum subthreshold amplitude.

Where the membrane is stimulated electrically, the impulse amplitude required to elicit a response is dependent upon a number of factors. First, is the duration of current flow. Since the total charge transferred is equal to the current amplitude times the pulse duration, increased stimulus duration is associated with a decrease in threshold current amplitude. Second, the percentage of applied current that actually traverses the membrane varies inversely with electrode size. Third, the percentage of applied current that actually traverses the membrane varies directly with the proximity of the electrode to the tissue. Fourth, the impulse amplitude required to elicit a response is dependent upon the timing of stimulation within the excitability cycle.

Throughout much of the heart are clumps and strands of specialized cardiac muscle tissue. This tissue comprises the cardiac conduction system and serves to initiate and distribute depolarization waves throughout the myocardium. Any interference or block in cardiac impulse conduction may cause an arrhythmia or marked change in the rate or rhythm of the heart

Sometimes a patient suffering from a conduction disorder can be helped by an artificial pacemaker. Such a device contains a small battery powered electrical stimulator. When the artificial pacemaker is installed, electrodes are generally threaded through veins into the right ventricle, or into the right atrium and right ventricle, and the stimulator is planted beneath the skin in the shoulder or abdomen. The leads are planted in intimate contact with the cardiac tissue. The pacemaker then transmits rhythmic electrical impulses to the heart, and the myocardium responds by contracting rhythmically. Implantable medical devices for the pacing of the heart are well known in the art and have been used in humans since approximately the mid 1960s.

Either cathodal or anodal current may be used to stimulate the myocardium. However anodal current is thought not to be useful clinically. Cathodal current comprises electrical pulses of negative polarity. This type of current depolarizes the cell membrane by discharging the membrane capacitor, and directly reduces the membrane potential toward threshold level. Cathodal current, by directly reducing the resting membrane potential toward threshold has a one-half to one-third lower threshold current in late diastole than does anodal

current. Anodal current comprises electrical pulses of positive polarity. The effect of anodal current is to hyperpolarize the resting membrane. On sudden termination of the anodal pulse, the membrane potential returns towards resting level, overshoots to threshold, and a propagated response occurs. The use of anodal current to stimulate the myocardium is generally discouraged due to the higher stimulation threshold, which leads to use of a higher current, resulting in a drain on the battery of an implanted device and impaired longevity. Additionally, the use of anodal current for cardiac stimulation is discouraged due to the suspicion that the anodal contribution to depolarization can, particularly at higher voltages, contribute to arrhythmogenesis.

Virtually all artificial pacemaking is done using stimulating pulses of negative polarity, or in the case of bipolar systems, the cathode is closer to the myocardium than is the anode. Where the use of anodal current is disclosed, it is generally as a charge of minute magnitude used to dissipate residual charge on the electrode. This does not affect or condition the myocardium itself. Such a use is disclosed in U.S. Patent No. 4,543,956 to Herscovici.

The use of a triphasic waveform has been disclosed in U.S. Patent Nos. 4,903,700 and 4,821,724 to Whigham et al., and U.S. Patent No. 4,343,312 to Cals et al. Here, the first and third phases have nothing to do with the myocardium per se, but are only envisioned to affect the electrode surface itself. Thus, the charge applied in these phases is of very low amplitude.

Lastly, biphasic stimulation is disclosed in U.S. Patent No. 4,402,322 to Duggan. The goal of this disclosure is to produce voltage doubling without the need for a large capacitor in the output circuit. The phases of the biphasic stimulation disclosed are of equal magnitude and duration.

What is needed is an improved means for stimulating muscle tissue, wherein the contraction elicited is enhanced and the damage to the tissue adjacent to the electrode is diminished.

Enhanced myocardial function is obtained through the biphasic pacing of the present invention. The combination of cathodal with anodal pulses of either a stimulating or conditioning nature, preserves the improved conduction and contractility of anodal pacing while eliminating the drawback of increased stimulation threshold. The result is a depolarization wave of increased propagation speed. This increased propagation speed

results in superior cardiac contraction leading to an improvement in blood flow. Improved stimulation at a lower voltage level also results in reduction in power consumption and increased life for pacemaker batteries. Lastly, the improved stimulation achieved through the practice of the present invention allows for cardiac stimulation without the necessity of placing electrical leads in intimate contact with cardiac tissue. Standard stimuli delivered to the cardiac blood pool are ineffective in capturing the myocardium because it does not meet the stimulation threshold. While voltage of the pulse generator can be increased, when it does capture it is often so high that it also stimulates skeletal muscles thereby causing a painful twitching of the chest wall when only the heart stimulation was desired. As will be further discussed, through the practice of the present invention, one can enhance myocardial function through cardiac blood pool stimulation.

As with the cardiac muscle, striated muscle may also be stimulated electrically, chemically, mechanically or by temperature change. Where the muscle fiber is stimulated by a motor neuron, the neuron transmits an impulse which activates all of the muscle fibers within its control, that is, those muscle fibers in its motor unit. Depolarization in one region of the membrane stimulates adjacent regions to depolarize also, and a wave of depolarization travels over the membrane in all directions away from the site of stimulation. Thus, when a motor neuron transmits an impulse, all the muscle fibers in its motor unit are stimulated to contract simultaneously. The minimum strength to elicit a contraction is called the threshold stimulus. Once this level of stimulation has been met, the generally held belief is that increasing the level will not increase the contraction. Additionally, since the muscle fibers within each muscle are organized into motor units, and each motor unit is controlled by a single motor neuron, all of the muscle fibers in a motor unit are stimulated at the same time. However, the whole muscle is controlled by many different motor units that respond to different stimulation thresholds. Thus, when a given stimulus is applied to a muscle, some motor units may respond while others do not.

The combination of cathodal and anodal pulses of the present invention also provides improved contraction of striated muscle where electrical muscular stimulation is indicated due to neural or muscular damage. Where nerve fibers have been damaged due to trauma or disease, muscle fibers in the regions supplied by the damaged nerve fiber tend to undergo atrophy and waste away. A muscle that cannot be exercised may decrease to half of its usual

size in a few months. Where there is no stimulation, not only will the muscle fibers decrease in size, but they will become fragmented and degenerated, and replaced by connective tissue. Through electrical stimulation one may maintain muscle tone, such that upon healing or regeneration of the nerve fiber, viable muscle tissue remains. Enhanced muscle contraction is obtained through the biphasic stimulation of the present invention. The combination of cathodal with anodal pulses of either a stimulating or conditioning nature results in contraction of a greater number of motor units at a lower voltage level, leading to superior muscle response.

SUMMARY OF THE INVENTION

It is therefore an object of the present invention to provide improved stimulation of cardiac tissue.

It is another object of the present invention to increase cardiac output through superior cardiac contraction leading to greater stroke volume.

It is another object of the present invention to increase impulse propagation speed.

It is another object of the present invention to extend pacemaker battery life.

It is a further object of the present invention to obtain effective cardiac stimulation at a lower voltage level.

It is a further object of the present invention to eliminate the necessity of placing electrical leads in intimate contact with tissue to obtain tissue stimulation.

It is a further object of the present invention to provide improved stimulation of muscle tissue.

It is a further object of the present invention to provide contraction of a greater number of muscle motor units at a lower voltage level.

A method and apparatus for muscular stimulation in accordance with the present invention includes the administration of biphasic stimulation to the muscle tissue, wherein both cathodal and anodal pulses are administered. According to one aspect of this invention, this stimulation is administered to the myocardium in order to enhance myocardial function. According to a further aspect of this invention, this stimulation is administered to the cardiac blood pool and thereafter conducted to the cardiac tissue. This enables cardiac stimulation

without the necessity of placing electrical leads in intimate contact with cardiac tissue. According to a still further aspect of this invention, the stimulation is administered to striated muscle tissue to evoke muscular response. Pacemaker electronics needed to practice the method of the present invention are well known to those skilled in the art. Current pacemaker electronics are capable of being programmed to deliver a variety of pulses, including those disclosed herein.

The method and apparatus of the present invention comprises a first and second stimulation phase, with each stimulation phase having a polarity, amplitude, shape and duration. In a preferred embodiment the first and second phases have differing polarities. In one alternative embodiment, the two phases are of differing amplitude. In a second alternative embodiment, the two phases are of differing duration. In a third alternative embodiment, the first phase is in a chopped wave form. In a fourth alternative embodiment, the amplitude of the first phase is ramped. In a fifth alternative embodiment the first phase is administered over 200 milliseconds after completion of a cardiac beating/pumping cycle. In a preferred alternative embodiment, the first phase of stimulation is an anodal pulse at maximum subthreshold amplitude for a long duration, and the second phase of stimulation is a cathodal pulse of short duration and high amplitude. It is noted that the aforementioned alternative embodiments can be combined in differing fashions. It is also noted that these alternative embodiments are intended to be presented by way of example only, and are not limiting.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is a schematic representation of leading anodal biphasic stimulation.

Fig. 2 is a schematic representation of leading cathodal biphasic stimulation.

Fig. 3 is a schematic representation of leading anodal stimulation of low level and long duration, followed by conventional cathodal stimulation.

Fig. 4 is a schematic representation of leading anodal stimulation of ramped low level and long duration, followed by conventional cathodal stimulation.

Fig. 5 is a schematic representation of leading anodal stimulation of low level and short duration, administered in series followed by conventional cathodal stimulation.

Fig. 6 graphs conduction velocity transverse to the fiber vs pacing duration resulting from leading anodal biphasic pulse.

Fig. 7 graphs conduction velocity parallel to the fiber vs pacing duration resulting from leading anodal biphasic pulse.

DETAILED DESCRIPTION

The present invention relates to the biphasic electrical stimulation of muscle tissue. Fig. 1 depicts biphasic electrical stimulation wherein a first stimulation phase comprising anodal stimulus **102** is administered having amplitude **104** and duration **106**. This first stimulation phase is immediately followed by a second stimulation phase comprising cathodal stimulation **108** of equal intensity and duration.

Fig. 2 depicts biphasic electrical stimulation wherein a first stimulation phase comprising cathodal stimulation **202** having amplitude **204** and duration **206** is administered. This first stimulation phase is immediately followed by a second stimulation phase comprising anodal stimulation **208** of equal intensity and duration.

Fig. 3 depicts a preferred embodiment of the present invention wherein a first stimulation phase comprising low level, long duration anodal stimulation **302** having amplitude **304** and duration **306** is administered. This first stimulation phase is immediately followed by a second stimulation phase comprising cathodal stimulation **308** of conventional intensity and duration. In an alternative embodiment of the invention, anodal stimulation **302** is at maximum subthreshold amplitude. In yet another alternative embodiment of the invention, anodal stimulation **302** is less than three volts. In another alternative embodiment of the invention, anodal stimulation **302** is a duration of approximately two to eight milliseconds. In yet another alternative embodiment of the invention, cathodal stimulation **308** is of a short duration. In another alternative embodiment of the invention, cathodal stimulation **308** is approximately 0.3 to 0.8 milliseconds. In yet another alternative embodiment of the invention, cathodal stimulation **308** is of a high amplitude. In another alternative embodiment of the invention, cathodal stimulation **308** is in the approximate range of three to twenty volts. In yet another alternative embodiment of the present invention,

cathodal stimulation **308** is of a duration less than 0.3 milliseconds and at a voltage greater than twenty volts. In another alternative embodiment, anodal stimulation **302** is administered over 200 milliseconds post heart beat. In the manner disclosed by these embodiments, as well as those alterations and modifications which may become obvious upon the reading of this specification, a maximum membrane potential without activation is achieved in the first phase of stimulation.

Fig. 4 depicts an alternative preferred embodiment of the present invention wherein a first stimulation phase comprising anodal stimulation **402** is administered over period **404** with rising intensity level **406**. The ramp of rising intensity level **406** may be linear or non-linear, and the slope may vary. This anodal stimulation is immediately followed by a second stimulation phase comprising cathodal stimulation **408** of conventional intensity and duration. In an alternative embodiment of the invention, anodal stimulation **402** rises to a maximum subthreshold amplitude. In yet another alternative embodiment of the invention, anodal stimulation **402** rises to a maximum amplitude that is less than three volts. In another alternative embodiment of the invention, anodal stimulation **402** is a duration of approximately two to eight milliseconds. In yet another alternative embodiment of the invention, cathodal stimulation **408** is of a short duration. In another alternative embodiment of the invention, cathodal stimulation **408** is approximately 0.3 to 0.8 milliseconds. In yet another alternative embodiment of the invention, cathodal stimulation **408** is of a high amplitude. In another alternative embodiment of the invention, cathodal stimulation **408** is in the approximate range of three to twenty volts. In yet another alternative embodiment of the present invention, cathodal stimulation **408** is of a duration less than 0.3 milliseconds and at a voltage greater than twenty volts. In another alternative embodiment, anodal stimulation **402** is administered over 200 milliseconds post heart beat. In the manner disclosed by these embodiments as well as those alterations and modifications which may become obvious upon the reading of this specification, a maximum membrane potential without activation is achieved in the first phase of stimulation.

Fig. 5 depicts biphasic electrical stimulation wherein a first stimulation phase comprising series **502** of anodal pulses is administered at amplitude **504**. In one embodiment rest period **506** is of equal duration to stimulation period **508** and is administered at baseline amplitude. In an alternative embodiment, rest period **506** is of a differing duration than

stimulation period **508** and is administered at baseline amplitude. Rest period **506** occurs after each stimulation period **508** with the exception that a second stimulation phase comprising cathodal stimulation **510** of conventional intensity and duration immediately follows the completion of series **502**. In an alternative embodiment of the invention, the total charge transferred through series **502** of anodal stimulation is at the maximum subthreshold level. In yet another alternative embodiment of the invention, the first stimulation pulse of series **502** is administered over 200 milliseconds post heart beat. In another alternative embodiment of the invention, cathodal stimulation **510** is of a short duration. In yet another alternative embodiment of the invention, cathodal stimulation **510** is approximately 0.3 to 0.8 milliseconds. In another alternative embodiment of the invention, cathodal stimulation **510** is of a high amplitude. In yet another alternative embodiment of the invention, cathodal stimulation **510** is in the approximate range of three to twenty volts. In another alternative embodiment of the invention, cathodal stimulation **510** is of a duration less than 0.3 milliseconds and at a voltage greater than twenty volts.

EXAMPLE 1

Stimulation and propagation characteristics of the myocardium were studied in isolated hearts using pulses of differing polarities and phases. The experiments were carried out in five isolated Langendorff perfused rabbit hearts. Conduction velocity on the epicardium was measured using an array of bipolar electrodes. Measurements were made between six millimeters and nine millimeters from the stimulation site. Transmembrane potential was recorded using a floating intracellular microelectrode. The following protocols were examined: monophasic cathodal pulse, monophasic anodal pulse, leading cathodal biphasic pulse and leading anodal biphasic pulse.

Table 1 discloses the conduction speed transverse to fiber direction for each stimulation protocol administered, with stimulations of three, four and five volts and two millisecond pulse duration.

TABLE 1

Conduction Speed Transverse to Fiber Direction, 2 msec duration

	3 V	4 V	5 V
Cathodal Monophasic	18.9 ± 2.5 cm/sec	21.4 ± 2.6 cm/sec	23.3 ± 3.0 cm/sec
Anodal Monophasic	24.0 ± 2.3 cm/sec	27.5 ± 2.1 cm/sec	31.3 ± 1.7 cm/sec
Leading Cathodal Biphasic	27.1 ± 1.2 cm/sec	28.2 ± 2.3 cm/sec	27.5 ± 1.8 cm/sec
Leading Anodal Biphasic	26.8 ± 2.1 cm/sec	28.5 ± 0.7 cm/sec	29.7 ± 1.8 cm/sec

Table 2 discloses the conduction speed along fiber direction for each stimulation protocol administered, with stimulations of three, four and five volts and two millisecond pulse duration.

TABLE 2

Conduction Speed Along Fiber Direction, 2 msec stimulation

	3 V	4 V	5 V
Cathodal Monophasic	45.3 ± 0.9 cm/sec	47.4 ± 1.8 cm/sec	49.7 ± 1.5 cm/sec
Anodal Monophasic	48.1 ± 1.2 cm/sec	51.8 ± 0.5 cm/sec	54.9 ± 0.7 cm/sec
Leading Cathodal Biphasic	50.8 ± 0.9 cm/sec	52.6 ± 1.1 cm/sec	52.8 ± 1.7 cm/sec
Leading Anodal Biphasic	52.6 ± 2.5 cm/sec	55.3 ± 1.5 cm/sec	54.2 ± 2.3 cm/sec

The differences in conduction velocities between the cathodal monophasic, anodal monophasic, leading cathodal biphasic and leading anodal biphasic were found to be significant ($p < 0.001$). From the transmembrane potential measurements, the maximum upstroke ($(dV/dt)max$) of the action potentials was found to correlate well with the changes in conduction velocity in the longitudinal direction. For a four volt pulse of two millisecond duration, $(dV/dt)max$ was 63.5 ± 2.4 V/sec for cathodal and 75.5 ± 5.6 V/sec for anodal pulses.

EXAMPLE 2

The effects of varying pacing protocols on cardiac electrophysiology were analyzed using Langendorff prepared isolated rabbit hearts. Stimulation was applied to the heart at a constant voltage rectangular pulse. The following protocols were examined: monophasic

anodal pulse, monophasic cathodal pulse, leading anodal biphasic pulse and leading cathodal biphasic pulse. Administered voltage was increased in one volt steps from one to five volts for both anodal and cathodal stimulation. Duration was increased in two millisecond steps from two to ten milliseconds. Epicardial conduction velocities were measured along and transverse to the left ventricular fiber direction at a distance between three to six millimeters from the left ventricular free wall. Figs. 6 and 7 depict the effects of stimulation pulse duration and the protocol of stimulation administered on the conduction velocities.

Fig. 6 depicts the velocities measured between three millimeters and six millimeters transverse to the fiber direction. In this region, cathodal monophasic stimulation **602** demonstrates the slowest conduction velocity for each stimulation pulse duration tested. This is followed by anodal monophasic stimulation **604** and leading cathodal biphasic stimulation **606**. The fastest conductive velocity is demonstrated by leading anodal biphasic stimulation **608**.

Fig. 7 depicts the velocities measured between three millimeters and six millimeters parallel to the fiber direction. In this region, cathodal monophasic stimulation **702** demonstrates the slowest conduction velocity for each stimulation pulse duration tested. Velocity results of anodal monophasic stimulation **704** and leading cathodal biphasic stimulation **706** are similar with anodal monophasic stimulation demonstrating slightly quicker speeds. The fastest conduction velocity is demonstrated by leading anodal biphasic stimulation **708**.

In one aspect of the invention, electrical stimulation is administered to the cardiac muscle. The anodal stimulation component of biphasic electrical stimulation augments cardiac contractility by hyperpolarizing the tissue prior to excitation, leading to faster impulse conduction, more intracellular calcium release, and the resulting superior cardiac contraction. The cathodal stimulation component eliminates the drawbacks of anodal stimulation, resulting in effective cardiac stimulation at a lower voltage level than would be required with anodal stimulation alone. This in turn, extends pacemaker battery life and reduces tissue damage.

In a second aspect of the invention, biphasic electrical stimulation is administered to the cardiac blood pool, that is, the blood entering and surrounding the heart. This enables cardiac stimulation without the necessity of placing electrical leads in intimate contact with

cardiac tissue, thereby diminishing the likelihood of damage to this tissue. The stimulation threshold of biphasic stimulation administered via the blood pool is in the same range as standard stimuli delivered directly to the heart muscle. Through the use of biphasic electrical stimulation to the cardiac blood pool it is therefore possible to achieve enhanced cardiac contraction, without skeletal muscle contraction, cardiac muscle damage or adverse effects to the blood pool.

In a third aspect of the invention biphasic electrical stimulation is applied to striated muscle tissue. The combination of anodal with cathodal stimulation results in the contraction of a greater number of muscular motor units at a lower voltage level, resulting in improved muscular response.

Having thus described the basic concept of the invention, it will be readily apparent to those skilled in the art that the foregoing detailed disclosure is intended to be presented by way of example only, and is not limiting. Various alterations, improvements and modifications will occur and are intended to those skilled in the art, but are not expressly stated herein. These modifications, alterations and improvements are intended to be suggested hereby, and within the spirit and scope of the invention. Further, the pacing pulses described in this specification are well within the capabilities of existing pacemaker electronics with appropriate programming. Accordingly, the invention is limited only by the following claims and equivalents thereto.

What is claimed is:

1. A method for electrical cardiac pacing comprising:

applying electrical stimulation to a cardiac blood pool.

2. The method for electrical cardiac pacing as in claim **1** wherein the electrical stimulation comprises:

a first stimulation phase with a first phase polarity, a first phase amplitude, a first phase shape and a first phase duration; and

a second stimulation phase with a second phase polarity, a second phase amplitude, a second phase shape and a second phase duration.

3. The method for electrical cardiac pacing as in claim **2**

wherein the first stimulation phase and the second stimulation phase are applied in sequence to the cardiac blood pool.

4. The method for electrical cardiac pacing of claim **2** wherein the first phase polarity is positive.

5. The method for electrical cardiac pacing of claim **2** wherein the first phase amplitude is less than the second phase amplitude.

6. The method for electrical cardiac pacing of claim **2** wherein the first phase amplitude is ramped from a baseline value to a second value.

7. The method for electrical cardiac pacing of claim **6** wherein the second value is equal to the second phase amplitude.

8. The method for electrical cardiac pacing of claim **2** wherein the first stimulation phase further comprises a series of stimulating pulses of a predetermined amplitude, polarity and duration.

9. The method for electrical cardiac pacing of claim **8** wherein the first stimulation phase further comprises a series of rest periods.

10. The method for electrical cardiac pacing of claim **9** wherein applying the first stimulation phase further comprises applying a rest period of a baseline amplitude after at least one stimulating pulse.

11. The method for electrical cardiac pacing of claim **10** wherein the rest period is of equal duration to the duration of the stimulating pulse.

12. The method for electrical cardiac pacing of claim **2** wherein the first phase amplitude is at a maximum subthreshold amplitude.

13. The method for electrical cardiac pacing of claim **12** wherein the maximum subthreshold amplitude is about 0.5 to 3.5 volts.

14. The method for electrical cardiac pacing of claim **2** wherein the first phase duration is at least as long as the second phase duration.

15. The method for electrical cardiac pacing of claim **2** wherein the first phase duration is about one to nine milliseconds.

16. The method for electrical cardiac pacing of claim **2** wherein the second phase duration is about 0.2 to 0.9 milliseconds.

17. The method for electrical cardiac pacing of claim **2** wherein the second phase amplitude is about two volts to twenty volts.

18. The method for electrical cardiac pacing of claim **2** wherein the second phase duration is less than 0.3 milliseconds and the second phase amplitude is greater than 20 volts.

19. The method for electrical cardiac pacing of claim **6** wherein the second value is at a maximum subthreshold amplitude.

20. The method for electrical cardiac pacing of claim **19** wherein the maximum subthreshold amplitude is about 0.5 to 3.5 volts.

21. The method for electrical cardiac pacing of claim **6** wherein the first phase duration is at least as long as the second phase duration.

22. The method for electrical cardiac pacing of claim **6** wherein the first phase duration is about one to nine milliseconds.

23. The method for electrical cardiac pacing of claim **6** wherein the second phase duration is about 0.2 to 0.9 milliseconds.

24. The method for electrical cardiac pacing of claim **6** wherein the second phase amplitude is about two volts to twenty volts.

25. The method for electrical cardiac pacing of claim **6** wherein the second phase duration is less than 0.3 milliseconds and the second phase amplitude is greater than 20 volts.

26. The method for electrical cardiac pacing of claim **2** wherein the first stimulation phase is initiated greater than 200 milliseconds after completion of a cardiac beating cycle.

27. A method for electrical cardiac pacing comprising the steps of:

defining a first stimulation phase with a positive polarity, a first phase amplitude, a first phase shape and a first phase duration, wherein said first phase amplitude is about 0.5 to 3.5 volts, wherein said first phase duration is about one to nine milliseconds and wherein said first stimulation phase is initiated greater than 200 milliseconds after completion of a cardiac beating cycle;

defining a second phase with a negative polarity, a second phase amplitude, a second phase shape and a second phase duration, wherein said second phase amplitude is about four volts to twenty volts and wherein said second phase duration is about 0.2 to 0.9 milliseconds; and

applying the first stimulation phase and the second stimulation phase in sequence to the cardiac blood pool.

28. A method for electrical cardiac pacing comprising the steps of:

defining a first stimulation phase with a first phase polarity, a first phase amplitude, a first phase shape and a first phase duration;

defining a second phase with a second phase polarity, a second phase amplitude, a second phase shape and a second phase duration; and

applying the first stimulation phase and the second stimulation phase in sequence to the cardiac blood pool.

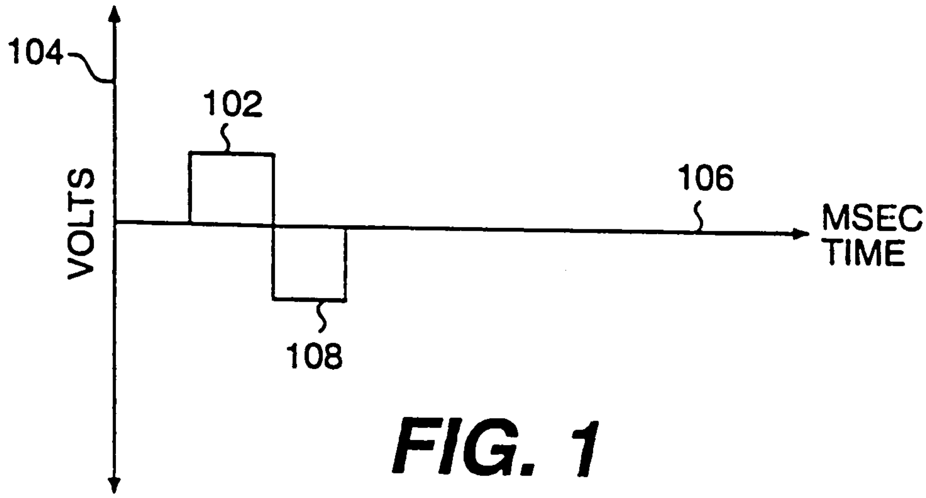
104
102
106
VOLTS
MSEC
TIME
108

FIG. 1

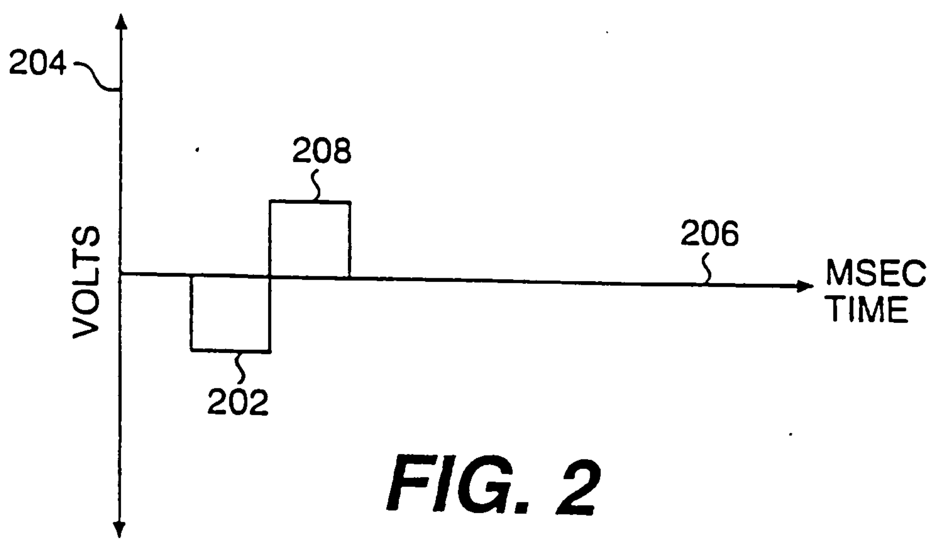
204
208
206
VOLTS
MSEC
TIME
202

FIG. 2

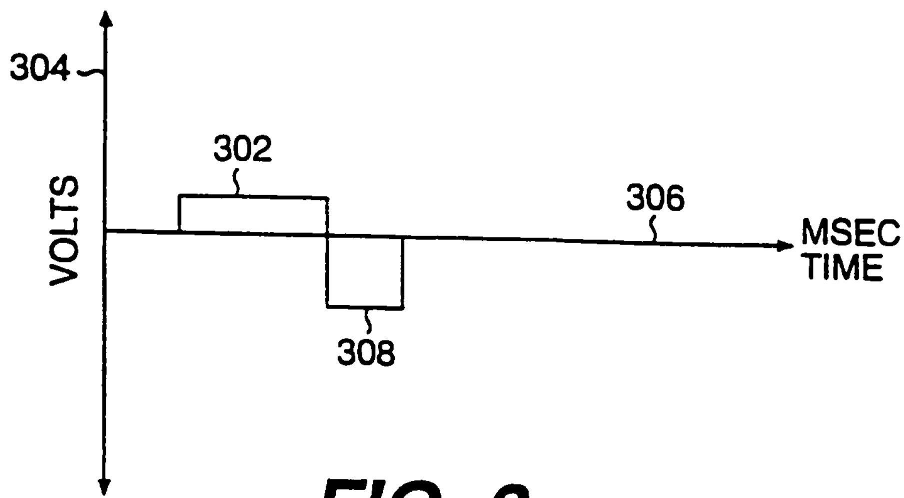
304
302
306
VOLTS
MSEC
TIME
308

FIG. 3

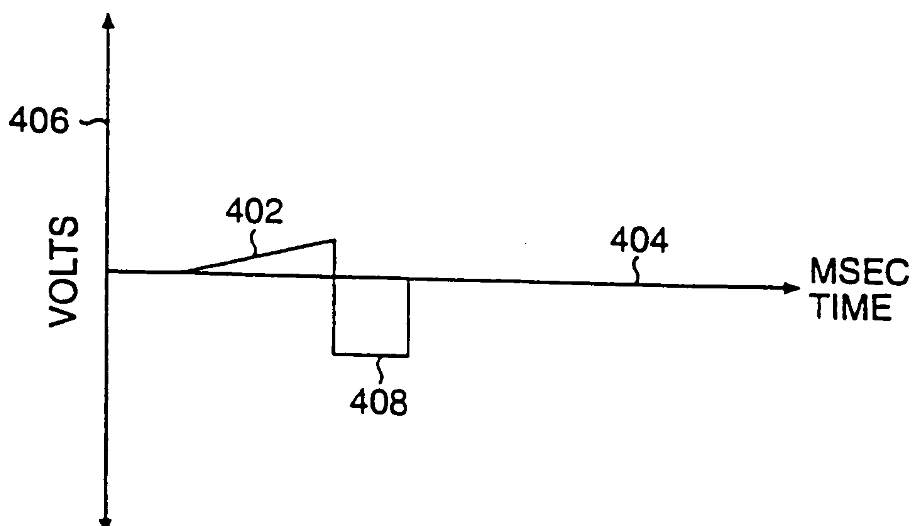
406
402
404
VOLTS
MSEC
TIME
408

FIG. 4

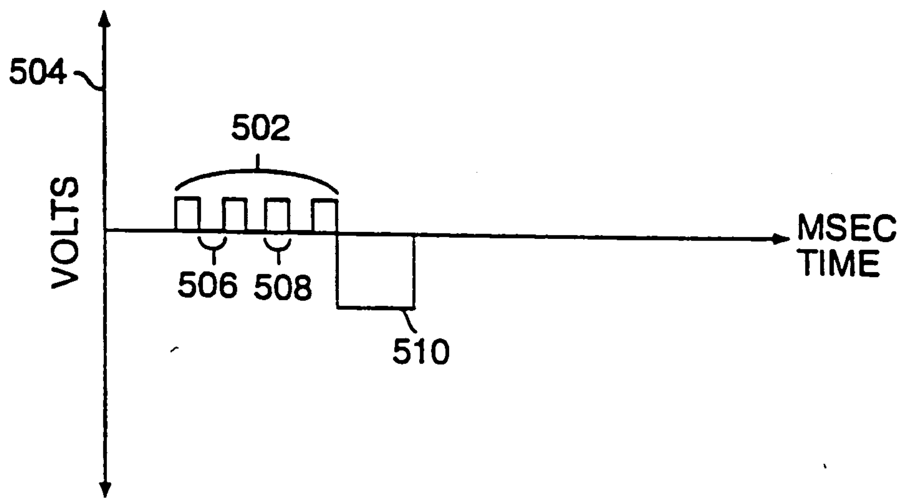

FIG. 5

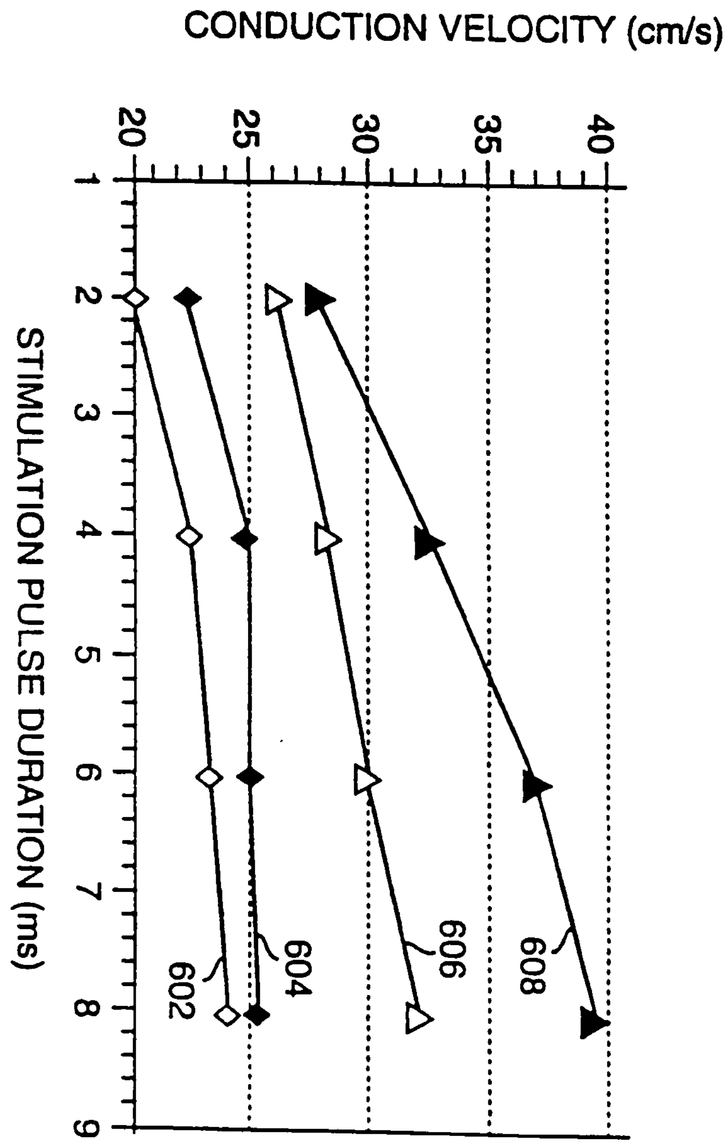
CONDUCTION VELOCITY (cm/s)
20
25
30
35
40
1
2
3
4
5
6
7
8
9
STIMULATION PULSE DURATION (ms)
602
604
606
608

FIG. 6

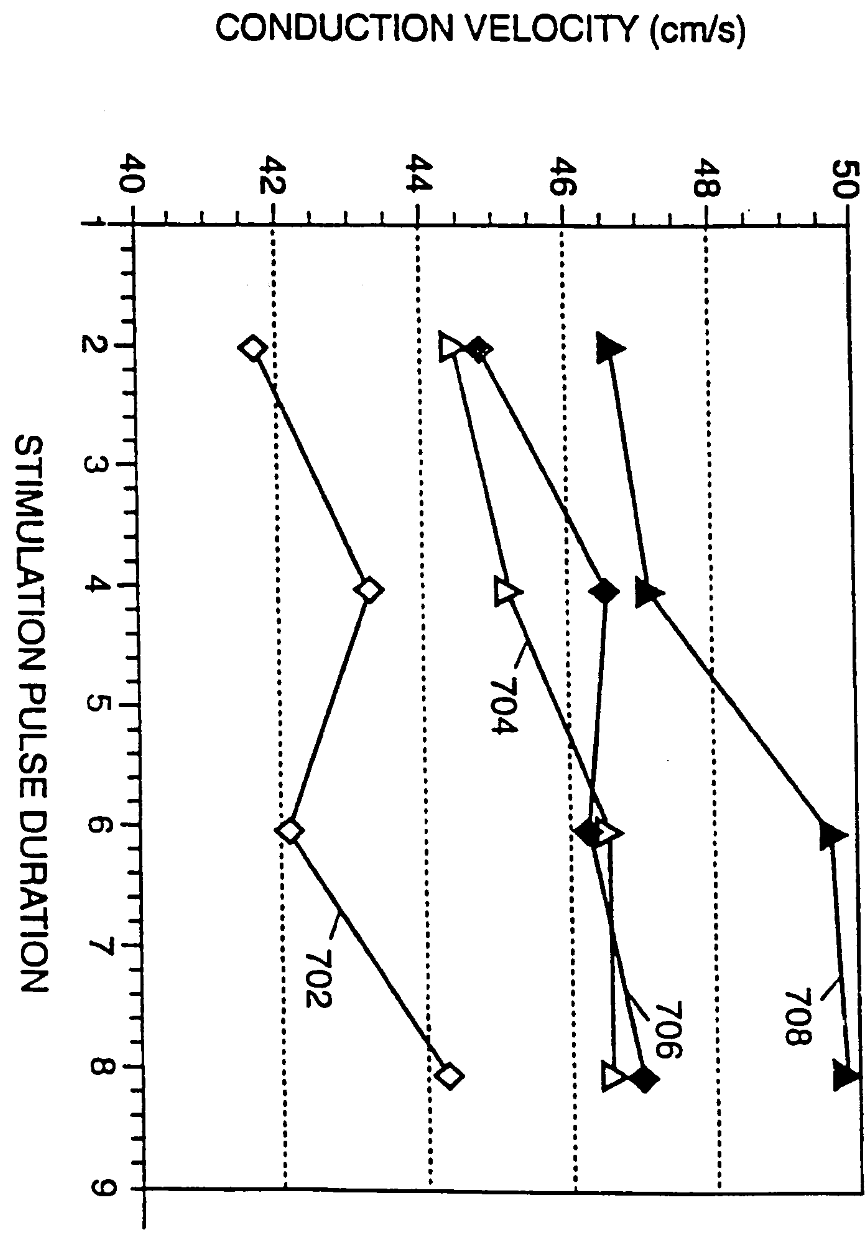
CONDUCTION VELOCITY (cm/s)
40
42
44
46
48
50
1
2
3
4
5
6
7
8
9
STIMULATION PULSE DURATION
702
704
706
708

FIG. 7

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/00879

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61N1/362

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	US 5 871 506 A (MOWER MORTON M) 16 February 1999 see the whole document ---	1,2
X	WO 97 25098 A (NEW TECHNOLOGIES SA YSY LTD ;FENSTER MAIER (IL); BEN HAIM SHLOMO ()) 17 July 1997 see the whole document see page 9, line 28 - line 30 see page 14, line 14 - line 20 see page 19, line 12 - line 15 see page 33, line 7 - line 18 see page 34, line 12 - line 23 ---	1,2

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 April 1999	26/04/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Ferrigno, A

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/00879

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 813 889 A (MEDTRONIC INC) 29 December 1997 see abstract see column 15, line 54 - column 16, line 11; figures ---	1,2
A	US 4 498 478 A (BOURGEOIS IVAN M) 12 February 1985 see the whole document -----	1,2

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 99/00879

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 3-28
because they relate to subject matter not required to be searched by this Authority, namely:
Rule 39.1(iv) PCT- Method for treatment of the human or animal body by therapy: an incomplete search, within the limit of the available documentation, has been carried out for claims 1 and 2.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 99/00879

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5871506 A	16-02-1999	NONE	
WO 9725098 A	17-07-1997	US 5738096 A	14-04-1998
		AU 1170197 A	01-08-1997
		AU 1170297 A	01-08-1997
		AU 1206697 A	01-08-1997
		AU 1206797 A	01-08-1997
		CA 2240943 A	17-07-1997
		CA 2242353 A	17-07-1997
		CA 2242356 A	17-07-1997
		EP 0888082 A	07-01-1999
		EP 0888150 A	07-01-1999
		WO 9724983 A	17-07-1997
		WO 9724981 A	17-07-1997
		WO 9725101 A	17-07-1997
		AU 3356797 A	02-04-1998
		AU 3356897 A	02-04-1998
		AU 3356997 A	02-04-1998
		AU 3357197 A	02-04-1998
		AU 3357297 A	02-04-1998
		WO 9810828 A	19-03-1998
		WO 9810829 A	19-03-1998
		WO 9810830 A	19-03-1998
		WO 9810831 A	19-03-1998
		WO 9810832 A	19-03-1998
		AU 1954597 A	22-08-1997
		WO 9727797 A	07-08-1997
EP 0813889 A	29-12-1997	US 5800465 A	01-09-1998
		JP 10052507 A	24-02-1998
US 4498478 A	12-02-1985	NONE	